UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/644,498	08/23/2000	Tuija Helina Salin-Nordstrom	2508.13US01	1667

24113 7590 11/20/2003

PATTERSON, THUENTE, SKAAR & CHRISTENSEN, P.A.
4800 IDS CENTER
80 SOUTH 8TH STREET
MINNEAPOLIS, MN 55402-2100

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/644,498	SALIN-NORDSTROM, TUIJA HELINA	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-12,15,16,23-32,34,35,38-43,46-59 and 64* is/are pending in the application.

4a) Of the above claim(s) *15,16,23,25-31,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-12,24,32,38-43,46-59 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 August 2003 has been entered.

Status of Application, Amendments, and/or Claims

2. Claims 1, 12, 57, and 64 have been amended. Claims 2, 3, 13, 14, 17-22, 33, 36, 37, 44, 45, and 60-63 have been cancelled. Claims 45, 16, 23, 25-31, 34, and 35 remain withdrawn from consideration. Claims 1, 4-12, 24, 38-43, 46-59, and 64 are under examination.

Withdrawn Rejections And/Or Objections

3. The Rejection of claim **12** under 35 U.S.C. 112 2 as set forth at pp. 17 33 in the previous Office Action (26 February 2003) is withdrawn in view of Applicant's amendments ().

Maintained Rejections And/Or Objections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The Rejection of claims **1, 4-12, 24, 38-43, 46-59,** and **64** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an in vitro method to produce a population that includes neurons and/or oligodendrocytes, the method comprising the following steps:*

(a) treating an in vitro cell culture of astrocytes derived from human neural progenitor cells with bFGF;

(b) said astrocytes are dissociated and plated;

(c) said astrocyte culture is maintained in MEDIUM I, II, or III without serum and treated with bFGF plus heparin for at least one day,

thereby producing a population of cells that include neurons and/or oligodendrocytes in addition, said method can be used as a control step to identify other compounds that may exert a similar transdifferentiation effect on said astrocytes, does not reasonably provide enablement for *using other astrocytes, growth factors, producing a second cell type, producing multipotent cell type, using other FGF family members, or method steps not herein included.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **use** the invention commensurate in scope with these claims for the reasons set forth at pp. 2-17 ¶5-32 of the previous Office Action (26 February 2003) in addition to the reasons set forth herein is maintained *in part*.

5. The Applicant traverses this rejection for the following reasons: **(a)** the claims as presently amended do not claim that non-neuronal cells must be necessarily derived from fully differentiated astrocytes, instead the present claims are directed to cultures that contain, but are not necessarily limited to, astrocytes, **(b)** one, but not the only, aspect of the presently claimed

inventions is that cultures having astrocytic cells may be used as part of a process or composition to produce the claimed cell types, **(c)** the claimed method is in contrast to methods that would require purified stem cell cultures, elaborate processes to capture stem cells, or complicated co-cultures of certain types of stem cells with certain other cell types, and **(d)** a person familiar with routine cell culture process could readily practice the instantly claimed invention.

6. These arguments have been taken into consideration and are not found persuasive for the following reasons.

7. The claims are drawn very broadly to methods of treating astrocytes with a FGF family member such that neurons, oligodendrocytes, a second unspecified cell type, and/or a multipotent cell type are produced {see Unsicker *et al.* (October 1992) "Molecular control of neural plasticity by the multifunctional growth factor families of the FGFs and TFG-βs." Annals of Anatomy **174**(5): 405-407}. The language of said claims encompasses practicing the invention using any known types of astrocytes, from any source, at any stage of development, to produce any "second cell type" which includes but is not limited to neurons, oligodendrocytes, and multipotent cell types.

8. The specification teaches that astrocytes that are: (a) derived from human neural progenitor cells, (b) dissociated, (c) plated, (d) treated/maintained in MEDIUM I, II, or III containing 20 ng/mL FGF plus heparin for 1 to 21 days produce a mixed culture. The resultant cell population includes neurons identified as β-tubulin III$^+$ and MAP2ab$^+$ (up to 30%), oligodendrocytes identified as CNPase$^+$ and O4$^+$ (up to 2%), and astrocytes identified as GFAP$^+$ (up to 80%). The Specification teaches that said method steps can be used to produce a cell

population that contains astrocytes, neurons, and oligodendrocytes and used as a control step for a screening method to identify compounds which cause "transdifferentiation" of said astrocytes.

9. However, the specification as filed fails to provide any guidance for the successful isolation of a "second cell type", a broad genus of cells which are as of yet undefined, or the production of "multipotent cells", another broad genus of cells for which the Specification is bereft of definition or guidance on how to produce using the instant teachings. Since resolution of the various complications in regards differentiation or transdifferentiation of astrocytes is highly unpredictable, as the multipotency/pluripotency of astrocytes is limited to "immature" or astrocytes from an early development stage (except for SVZ astrocytes), one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation.

10. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations with other members of the FGF family to correlate with successful production of a mixed cell culture. In addition, as discussed below, astrocytes are limited in their ability to produce other cells types (with the exception of SVZ astrocytes of which the Applicant has maintained that the instant astrocytes are not derived in previous Response filed 27 December 2002). In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

11. Additionally, a person skilled in the art would recognize that predicting the efficacy of using any astrocyte type based solely on the performance of a single type is highly problematic

(see MPEP §2164.01). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods using other FGF family members than bFGF, or any given astrocyte type, such a disclosure would not be considered enabling since the state of cell differentiation and transdifferentiation is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

12. The following references are cited herein to illustrate the state of the art of astrocytes.

13. On the breadth of the claims, US 6,040,180 (21 March 2000) Johe teaches that maintaining and differentiating CNS stem cells is neither predictable nor obvious to those skilled in the art (Col. 7 lines 53-60). This is taken in light of the instant invention as analogous art because the breadth of the claims as written implies the astrocytes used are capable of producing "multipotent cell types" and as such share properties with CNS stem cells, notorious in the art as difficult to maintain and differentiate. Thus the scope of the claims is too broad and hence unwieldy for one skilled in the art to successfully practice to its full extent as written (see also Gage *et al.* (1995) "Isolation, Characterization, and Use of Stem Cells from the CNS." Annu. Rev. Neurosci. **18**: 159-162 for the broad plain meaning of "multipotent cell type" in the art).

14. On the nature of the invention, the instant application as presented broadly reads on using any member of the FGF family to treat any astrocyte in such a manner as to transdifferentiate said astrocytes into neurons, oligodendrocytes, second cell type, and/or multipotent cell type. While is clear from the prior art that while some astrocytes are multipotent, not all astrocytes are {see Lee *et al.* (2000) "Gliogenesis in the Central Nervous System." Glia **30**: 105-121}. Further, it is also clear from the art that the FGF family of growth factors varies widely in its effects on the differentiation and/or growth of cells {see Bikfalvi *et al.* (1997) "Biological Roles of Fibroblast Growth Factor-2." Endocrine Reviews **18**(1): 26-45}. It is evident from the Specification as filed that the Applicant has used "young" or "immature" astrocytes derived directed from human neural precursor cells to practice the invention as demonstrated in 6. 0 Example 1 of the instant Specification. Thus it became clear that the invention could be successfully practiced if using these "young" astrocytes as opposed to using adult astrocytes, with the exception of subventricular zone astrocytes (SVZ), are not multipotent {see Rao (1999) "Multipotent and Restricted Precursors in the Central Nervous System." The Anatomical Record (New Antat.) **257**: 137-148}. This has been demonstrated by Laywell *et al.* (5 December 2000) "Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain." PNAS **97**(25): 13883-13888 who teaches that: "...astrocyte multipotency is restricted to early postnatal ages, except for SEZ astrocytes, which retain this ability in the mature brain." (pp. 13883). The Applicant, however, maintained in previous Response/Amendment(s) that the term "astrocyte" should not be read as included SEZ astrocytes nor does the Specification teach the use of said astrocyte subpopulation. Therefore only astrocytes derived directly from human

neural precursor cells in vitro can be used to practice the instant invention as shown in the instant Specification and confirmed by Laywell *et al.* to exhibit multipotency.

15. On the state of the prior art, Gaul and Lübbert (1992) "Cortical astrocytes activated by basic fibroblast growth factor secrete molecules that stimulate differentiation of mesencephalic dopamingergic neurons." Proceedings of the Royal Society of London **249**(1324): 57-63 teach that treatment of an astrocyte culture with 50 ng/mL of bFGF resulted in reactive gliosis and not transdifferentiation. Thus the prior art teaches that the invention is not viable with any given astrocyte culture as the cultures used by Gaul and Lübbert were from rat cortices. Further, Richards *et al.* (15 September 1992) "*De novo* generation of neuronal cells from the adult mouse brain." PNAS **89**(18): 8591-8595 teaches that bFGF treatment of brain cultures containing the cerebral cortex, hippocampus, diencephalons, striatum, and septum when treated with bFGF produced cells with neuronal morphology (pp. 8591). It is noted that the instant invention, as broadly claimed, would encompass astrocytes from these areas but the prior art does not teach that bFGF treatment lead astrocytes to produce the neuronal cells, but progenitor cells (pp. 8594). Further, cultures maintained in serum did not yield any neurons. It is also noted that the large brain sections include the subventricular zone (SVZ) an area known to harbor multipotent astrocytes and other progenitor cells. In addition, Raad *et al.* (October 1991) "Astrocyte-derived TGF-β2 and NGF Differentially Regulate Neural Recognition Molecule Expression by Cultured Astrocytes." The Journal of Cell Biology **115**(2): 473-484 teaches that treatment of immature and mature rat astrocytes with bFGF, among other growth factors, affects N-CAM and AMOG expression but does not provide support for transdifferentiation of said astrocytes upon treatment with bFGF (Figures 1, 3, and 4).

16. On the predictability in the art, Sweetnam *et al.* (July 1991) "Differential Effects of Acidic and Basic Fibroblast Growth Factors on Spinal Cord Cholinergic, GABAergic, and Glutamatergic Neurons." Journal of Neurochemistry **57**(1): 237-249 teaches that astrocyte cultures procured from embryonic day 12.5 Sprague-Dawley rats do not form neurons, oligodendrocytes, multipotent cell types, or second cell types when treated with aFGF (also known as FGF-1) and bFGF (also known as FGF-2) (Figures 6 and Table 1). Both FGF family members were mitogenic with aFGF increasing the thickness and branching of GFAP filaments (pp. 245). In addition, Morrison *et al.* (September 1988) "Basic fibroblast growth factor and epidermal growth factor exert differential trophic effects on CNS neurons." Journal of Neuroscience Research **21**(1): 71-79 teaches that treatment of primary cultures of astrocytes treated with 0.1, 0.5, 1.0, and 5.0 ng/mL of bFGF proliferated in a dose-dependent manner but did not produce any other cell types (Table I). Thus based on the prior art one skilled in the art would predict that FGF treated astrocytes would proliferate and increase GFAP intensity.

17. On the amount of guidance in the prior art, Walicke and Baird (1 May 1988) "Neurotrophic effects of basic and acidic fibroblast growth factors are not mediated through glial cells." Developmental Brain Research **468**(1): 71-79 teaches the establishment of an astrocyte culture from cerebral cortices of 1-3 day old rat pups which were grown in culture and dissociated (pp. 72). These astrocyte cultures are then maintained in serum-free DMEM and treated with 0 pg/mL to 1000 pg/mL of FGF which lead to their proliferation (Figure 1). Walicke and Baird, however, do not teach that this demonstration of an embodiment of the invention as claimed lead to the production of neurons, oligodendrocytes, multipotent cells, or "second cell types".

18. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of differentiating astrocytes to produce a population of cells that include neurons and/or oligodendrocytes as exemplified in the references herein.

New Rejections And/Or Objections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claim **12** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the term "second cell type" is not clear from the Specification or the prior art.

20. Claim **47** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 47 recites the limitation "pretreatment step" in the first line. There is insufficient antecedent basis for this limitation in the claim.

Summary

21. Claims **1, 4-12, 24, 38-43, 46-59,** and **64** are hereby rejected.

22. The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

a. US 6361996 (26 March 2002) Rao & Mayer-Proschel

b. US 5,753,506 (19 May 1998) Johe

c. US 2003/0032181 (13 February 2003) Weiss & Gregg

d. US 2003/0109041 (12 June 2003) Rao *et al.*

e. US 2003/0059939 (27 March 2003) Page *et al.*

f. Gray and Patel (6 March 1992) "Characterization of a neurotrophic factor produced by cultured astrocytes involved in the regulation of subcortical cholinergic neurons." Brain Research **574**(1-2): 257-265

g. Seidman *et al.* (4 April 1997) "Isolation, cloning and characterization of a putative type-1 astrocyte cell line." Brain Research **753**(1): 18-26

h. Petroski *et al.* (September 1991) "Basic Fibroblast Growth Factor Regulates the Ability of Astrocytes to Support Hypothalamic Neuronal Survival *in Vitro*." Developmental Biology **147**(1): 1-13

i. Sultana *et al.* (April 2000) "Intermediate Filament Protein Synemin is Transiently Expressed in a Subset of Astrocytes During Development." Glia **30**(2): 143-153

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C Kemmerer

CJN
November 12, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER